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Mestrado Integrado em Medicina

Prognostic Value of Diabetes in Post-Acute Myocardial Infarction Patients with Preserved Left Ventricle Ejection Fraction.

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Prognostic Value of Diabetes in Post-Acute Myocardial Infarction Patients with Preserved Left Ventricle Ejection Fraction

Artigo de Investigação Médica

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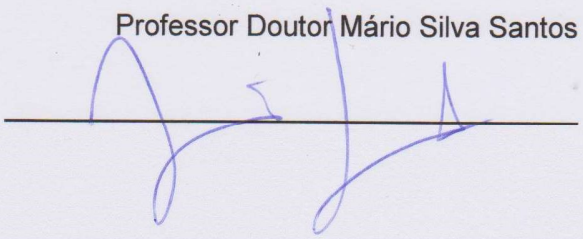

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Abbreviations

AF - Atrial Fibrillation

AMI - Acute Myocardial Infarction

CHD - Coronary Heart Disease

CK - Creatinine-Kinase

CR - Cardiac Rehabilitation

CVD - Cardiovascular Disease

HFpEF - Heart Failure with preserved Ejection Fraction

HR - Heart Rate

eGFR - estimated Glomerular Filtration Rate

LVEF - Left Ventricle Ejection Fraction

PCI - Percutaneous Coronary Intervention

SCD - Sudden Cardiac Death

STEMI - ST-segment Elevation Myocardial Infarction

RESUMO

Introdução: A diabetes tem sido associada a mau prognóstico cardiovascular. No entanto, escassos estudos têm sido desenvolvidos em pacientes pós enfarte agudo do miocárdio que evoluem com função cardíaca preservada. O objetivo deste trabalho é descrever as correlações clínicas e valor prognóstico da diabetes em pacientes pós-enfarte agudo do miocárdio (EAM) em pacientes que evoluem com fração de ejeção do ventrículo esquerdo preservada (FEVE).

Métodos: Estudamos doentes referenciados para o programa de reabilitação cardíaca após enfarte agudo do miocárdio, entre Janeiro de 2010 e Dezembro de 2012. Estes tinham de ter fração de ejeção do ventrículo esquerdo >=50% à data da alta (medida por ecocardiografia transtorácica) e completado o programa de reabilitação cardíaca. Os dados laboratoriais foram colhidos a partir de medição de análises sanguíneas durante o internamento. O outcome composto foi definido como morte de qualquer causa, hospitalização por insuficiência cardíaca, diagnóstico de novo ou agravamento da insuficiência cardíaca no doente seguido em ambulatório.

Resultados: Os 336 doentes estudados tinham uma média de idades de 60 ±11 anos e 76% eram do sexo masculino. 31% eram diabéticos e 75% tinham dislipidémia, hipertensão (61%) e história passada ou presente de tabagismo (63%) foram fatores de risco cardiovascular prevalentes. A diabetes estava associada com idade mais avançada (63 anos ± 10 vs 58 ± 11), sexo feminino (34% vs 19%, p=0.002), um maior índice de massa corporal (28 ± 4 vs 26 ± 4, p<0.001) e história de hipertensão (80% vs 53%, p<0.001). Estes pacientes tiveram também classificações de Killip mais altas (Classe de Killip ≥II 18% vs 6%, p=0.001).

Conclusão: Em pacientes pós enfarte agudo do miocárdio com fração de ejeção do ventrículo esquerdo preservada, a diabetes está associada a pacientes mais frágeis, doença arterial coronária mais severa e incidência mais alta de insuficiência cardíaca durante a hospitalização. Diabetes foi a única característica clínica capaz de predizer o prognóstico neste grupo heterogéneo de pacientes.

Termos MeSH: Enfarte do Miocárdio, Disfunção Ventricular, Esquerda; Diabetes Mellitus ; Insuficiência Cardíaca

ABSTRACT

Introduction: Diabetes has long been associated with adverse cardiovascular outcomes. Scarce data is available on the clinical significance of this prevalent comorbidity in post-acute myocardial infarction (AMI) patients who evolve with preserved cardiac function. We aimed to describe the clinical correlates and prognostic value of diabetic status in post-AMI patients evolving with preserved Left Ventricular Ejection Fraction.

Methods: We studied patients referred to a cardiac rehabilitation (CR) program after an acute myocardial infarction (AMI) between January 2010 and December 2012. They had to have a Left Ventricle Ejection Fraction >=50% at the time of hospital discharge (measured by transthoracic echocardiography) and completed cardiac rehabilitation program. The laboratorial data was collected from blood analysis measurement during hospitalization. The composite outcome was defined as all-cause death, heart failure hospitalization, de novo diagnosis or worsening HF at the outpatient clinic, and it was assessed by chart review.

Results: The 336 studied patients had a mean age of 60 ±11 years and 76% were male. 31% were diabetic and 75% had dyslipidemia, hypertension (61%) and present or past smoking (63%) were prevalent cardiovascular risk factors. Diabetic status was associated with older age (63y ± 10 vs 58 ± 11), female gender (34% vs 19%, p=0.002), higher body mass index (28 ± 4 vs 26 ± 4, p<0.001) and a history of hypertension (80% vs 53%, p<0.001). They also evolved with higher Killip classes (Killip class ≥II 18% vs 6%, p=0.001).

Conclusion: In post-acute myocardial infarction patients with preserved left ventricle ejection fraction, diabetic status is associated with more fragile patients, severe coronary artery disease and higher incidence of heart failure during hospitalization. Diabetes was the only clinical feature to predict outcome in this heterogeneous group of patients.

MeSH terms: Myocardial Infarction; Ventricular Dysfunction, Left ; Diabetes Mellitus ; Heart Failure

INTRODUCTION

Diabetes is one of the most prevalent chronic diseases worldwide and has a growing incidence [1-3]. Diabetics have a heightened risk of developing cardiovascular disease (CVD) [4-7], and among those with established CVD it is associated with worse prognosis. Approximately 40% to 50% of patients with coronary heart disease (CHD) have type 2 diabetes [8]. In this subset of patients, it increases the risk of having an acute coronary syndrome and the risk of dying [9-11]. In heart failure with reduced ejection fraction, diabetes increases the risk of cardiovascular mortality, hospitalization and sudden death. In heart failure with preserved ejection fraction (HFpEF), diabetics might represent a distinct phenotype characterized by specific functional and prognostic features [12]. New drugs recently approved for treatment of diabetes [13-15] impressively reduced cardiovascular death and heart hospitalizations, opening new windows of opportunity to minimize cardiovascular outcomes in diabetics.

Advances in pharmacological and mechanical reperfusion of acute myocardial infarction (AMI) over the past decades led to a significant improvement in survival and to an increasing proportion of post-AMI patients evolving with preserved left ventricle ejection fraction LVEF[16]. These patients have a better prognosis than those with reduced LVEF [17], however their clinical course is not as benign as previously presumed [17, 18]. Sudden cardiac death (SCD) incidence in this subgroup represent the greatest absolute number of SCD in the post-AMI setting [19]. Atrial fibrillation (AF) – an important prognostic marker in cardiovascular disease patients – complicates the clinical course of up to 58% of patients with preserved LVEF during the 2 years following an AMI [20]. Scarce data is available about the prognostic value of diabetic status in post-AMI patients evolving with preserved LVEF.

In this study, we aimed to describe the clinical correlates and prognostic value of diabetic status in post-AMI patients with preserved LVEF.

METHODS

We studied 336 consecutive patients that completed a cardiac rehabilitation program after an acute myocardial infarction (AMI) between January 2010 and December 2012 at Centro Hospitalar do Porto (Porto, Portugal).

We excluded patients with LVEF < 50% at the time of discharge.

Clinical, laboratorial, and echocardiographic data were collected by chart review. Supine transthoracic echocardiography was performed in all patients before the hospital discharge. LVEF was either calculated using the biplane Simpson method or eyeballing. Dimensions and volumes of cardiac chambers and left ventricular mass were measured according to current international recommendations [21]. The laboratorial data was collected from blood analysis measurement during hospitalization. NT-proBNP was measured using the Roche® NT-proBNP assay. Anemia was defined as hemoglobin less than 12 g/dL for women and less than 13 g/dL for men. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/ 1.73 m2.

Incident outcome events were defined as the first occurrence of all-cause death, heart failure hospitalization, or AMI. All events were collected by chart review.

This study conforms with the principles outlined in the Declaration of Helsinki and was approved by the institution's ethical committee (N/REF.ª 2016.236/199-DEFI/188-CES).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed data or median [25th, 75th percentiles] for non-normally distributed data. Categorical variables are expressed as number of subjects and proportion [n (%)]. Comparisons between groups were performed using 2-sided unpaired or paired t tests or Wilcoxon rank sums test for normally and non-normally distributed data, respectively. Fisher's exact test was applied to compare proportions. One-way ANOVA with Bonferroni correction was used to perform multiple group comparisons. Correlations between hemodynamic and metabolic variables were determined using Pearson or Spearman correlation for normally and non-normally distributed data, respectively. We used univariate and multivariable Cox proportional hazards regression models to study the relationship between diabetes and the composite outcome. Statistical analysis was performed using Stata software Version 12.1 (Stata Corp LP, College Station, TX, USA). A two-sided p-value <0.05 was considered significant.

RESULTS

Studied population

Clinical and demographic characteristics of the studied population are summarized in Table I. Of the 336 studied patients, 99 (31%) were diabetic. Most patients were male (76%) and had a mean age of 59±11 years. Dyslipidemia (75%), hypertension (61%), present or past smoking (63%) and diabetes (29%) were the most common cardiovascular risk factors. Eighteen per cent had previously been diagnosed with CAD. Clinical presentation with an ST-segment elevation myocardial infarction (STEMI) represented 44% of the overall patients. Three-vessel CAD was seen in a third of the patients. Left anterior descendent was the culprit vessel in 41% of the patients and percutaneous coronary intervention (PCI) was performed in 88% of them. The median and interquartile range of peak values of troponin and creatinine-kinase (CK) were 2.63 ng/mL and 900 U/L, respectively. The echocardiographic characteristics of the overall patients are displayed in Table II. During the index hospitalization, almost 8% of patients showed signs and symptoms of heart failure (6% in Killip class II and 2% in class III). At the time of discharge, more than 96% of the patients were medicated with dual antiplatelet therapy and statins. Medication at discharge is displayed in Table I.

Clinical and echocardiographic correlates of diabetes

Diabetic status was associated with older age (63y ± 10 vs 58y ± 11, p< 0.001), female gender (34% vs 19%, p=0.002), higher body mass index (28±4 vs 26±4, p< 0.001) and a history of hypertension (80% vs 53%, p<0.001). Diabetic patients were more likely to present with a non-ST segment elevation myocardial infarction (65% vs 52%, p=0.035), and they had significantly lower troponin T (0.4 [0.0-1.6] vs 1.2 [0.2–3.2] ng/mL, p< 0.001) and creatine kinase peak concentration (251 [91-840] vs 456 [161-1436] U/L, p=0.002) when compared to non-diabetic patients. They evolved with higher Killip classes (Killip class ≥II 18% vs 6%, p=0.001) and were more likely to need diuretic treatment at hospital discharge (12% vs 4%, p=0.005).

No significant differences between groups were observed regarding cardiac phenotype assessed by echocardiography (volumes and dimensions, segmental motion abnormalities and left ventricular remodeling pattern) at hospital discharge.

Prognostic value of diabetes

Over a follow-up of 3.7±1.8 years, composite outcome occurred in 24 (7%) patients (14 deaths, 4 HF hospitalizations and 6 acute coronary syndromes). The overall incident rate was 2.0 events per 100 000 person-years. Diabetics had an almost 4-fold

risk of having an adverse event during the follow-up (HR 3.75; 95%CI 1.64-8.57; p=0.002). After adjusted for age and sex, diabetes remained an independent risk factor (HR 3.44; 95%CI 1.46-8.09; p= 0.005).

DISCUSSION

In the studied post-AMI with preserved LVEF patients, a third were diabetic. These were older, more likely to be female and had increased BMI and dyslipidemia prevalence. Despite more severe CAD, diabetics were more likely to have a NSTEMI, had reduced myocardial infarction size as assessed by peak troponin but higher incidence of heart failure during hospitalization. Diabetes independently predicted prognosis, signalling a 3-fold increase risk of composite outcome.

The results showed that the incidence of type 2 diabetes is significantly higher in individuals aged >60 years and female gender is the most affected by this disease. This data were concordant with the last edition of IDF Diabetes Atlas[1]. Cardiovascular risk factors were also more often seen in this patients, such as high BMI, hypertension and dyslipidemia[22]. The characteristics of our study population are similar with the previous studies with patients with cardiovascular disease[23-26].

Atherosclerosis is the major disease process of CAD[27]. Dyslipidemia has an important role in pathogenesis of atherosclerosis[28]. So, attending to the highly correlation between diabetes and dyslipidemia[29] and to chronic inflammation present in diabetes[30-36] it culminates in a high risk of cardiovascular events. Which agrees with other data which shows CAD as the most common cause of death in patients with type 2 diabetes with almost 70% of cases[37].

Our data indicate that diabetics had higher Killip class during hospitalization which means worst prognosis. Available data about hospitalization in diabetics shows higher length of stay in this patients comparing with patients without diabetes[38, 39]. However there aren't studies using the Killip classification.

Besides diabetes, this patients tend to be older and have more cardiovascular risk factors such as dyslipidemia or hypertension as shows our study, which confers to these patients a more fragile status. By itself this could justify a worst prognosis in these patients however diabetes can lead to a cardiac contractile dysfunction not related with coronary artery disease but consequence of mitochondrial deterioration[40-42]. A recent study showed that diabetic rats exhibited ventricular systolic and diastolic dysfunction when hearts were exposed to overload comparing to controls[43] so we may be facing a new cardiac phenotype dysfunction.

Diabetes is nowadays a major public health problem, affecting millions of people worldwide and being currently the most costly disease in the US health care system[44]. In the AMI setting, patients with diabetes have higher mortality rates during the acute phase and in the long term[45]. Moreover, CVD is the most common cause of morbidity and mortality among the diabetic population[46]

Therefore, diabetic patients might benefit from more aggressive treatment of CAD, particularly those with multivessel coronary disease[47-49] and intensive intervention on risk factors.

Recently, new antidiabetic drugs such as SGLT-2 inhibitors have demonstrated beneficial effects on cardiovascular risk among patients with diabetes mellitus.

The improvement in cardiovascular (CV) outcomes was first observed in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study which demonstrated that the addition of empagliflozin to the antidiabetes treatment reduces CV mortality by 38% in type 2 diabetes mellitus patients with high CV risk[50]. Later, Canagliflozin was shown to reduce the composite endpoint of CV mortality, nonfatal myocardial infarction (MI), or nonfatal stroke in 14%[51]. Recently, the class effect of SGLT2 inhibitors on CV events reduction was also confirmed in new analyses of the The Comparative Effectiveness of Cardiovascular Outcomes (CVD-REAL) study with real world data from more 300,000 patients with T2DM across 6 countries[52].

Our study has several limitations that should be considered. The study has a retrospective design with a relatively small cohort size from a single centre. These features limit the statistical power and the generalizability of our findings. Also, the most fragile patients with more comorbidities are less likely to complete cardiac rehabilitation program. Therefore, using this approach we did not studied a representative sample of AMI patients and increased the risk of selection bias.

CONCLUSION

In post-AMI patients with preserved LVEF, diabetic status is associated with more fragile patients, severe CAD and higher incidence of HF during hospitalization. Diabetes was the only clinical feature to predict outcome in this heterogeneous group of patients.

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TABLES

Table I – Clinical characteristics of studied patients.

Characteristic	**Overall (n=336)**	**Non-diabetic patients (n=227)**	**Diabetic patients (n=99)**	**P-value**
Age, y	59.50 ± 10.97	58.16 ± 11.20	62.52 ± 9.86	< 0.001
Male, n (%)	253 (76%)	184 (81%)	65 (66%)	0.002
BMI, Kg/m2	26.56± 3.88	25.98 ± 3.85	27.82 ± 3.59	< 0.001
Hypertension, n (%)	201 (61%)	120 (53%)	79 (80%)	< 0.001
Smoking status Never smoked, n (%) Past smoker, n (%) Current smoker, n (%)	 122 (37%) 81 (25%) 124 (38%)	 75 (33%) 54 (24%) 97 (43%)	 46 (47%) 27 (27%) 26 (26%)	0.23
Dyslipidemia, n (%)	245 (75%)	163 (72%)	80 (82%)	0.07
History of atrial fibrillation, n (%)	5 (2%)	1 (2%)	3 (8%)	0.11
History of heart failure, n (%)	3 (1%)	3 (1%)	2 (2%)	0.64
Stroke, n (%)	10 (3%)	6 (3%)	4 (4%)	0.51
CAD, n (%)	59 (18%)	40 (18%)	17 (17%)	0.91
COPD, n (%)	12 (4%)	6 (3%)	6 (6%)	0.13
OSA, n (%)	4 (1%)	3 (1%)	1 (1%)	0.81
ACS hospitalization features				
STEMI, n (%)	143 (44%)	108 (48%)	34 (35%)	0.035
Killip class II, n (%) III, n (%) IV, n (%)	 16 (6%) 5 (2%) 3 (1%)	 8 (4%) 1 (1%) 1 (1%)	 8 (10%) 4 (5%) 2 (3%)	0.001
Number of coronaries with significant disease One-vessel, n (%)	 113 (36%)	 83 (38%)	 29 (30%)	0.047

Two-vessel, n (%) Three-vessel, n (%)	99 (31%) 105 (33%)	70 (32%) 65 (30%)	27 (28%) 40 (42%)	
Culprit coronary LAD, n (%) RCA, n (%) LCx, n (%)	127 (41%) 114 (37%) 70 (22%)	84 (39%) 79 (36%) 53 (24%)	41 (45%) 35 (38%) 16 (17%)	0.74
PCI, n (%)	286 (88%)	196 (88%)	87 (89%)	0.84
Atrial fibrillation, n (%)	12 (4%)	8 (4%)	3 (3%)	0.82
Blood analysis at discharge				
GFR, mL/min/1.73 m2	85.41 ± 18.56	86.19 ± 17.67	83.99 ± 20.29	0.34
GFR < 60 mL/min/1.73 m2, n (%)	32 (10%)	19 (8%)	12 (12%)	0.30
Hb, g/dL	13.44 ± 1.44	13.50 ± 1.33	13.33 ± 1.67	0.35
Anemia, n (%)	58 (25%)	54 (24%)	24 (24%)	0.95
Peak CK, U/L	899.88 ± 1179.72	456 [161-1436]	251 [91-840]	0.002
Peak TnT, ng/mL	2.63 ± 4.55	1.2 [0.2 – 3.2]	0.4 [0.0-1.6]	< 0.001
NT-Pro-BNP, ng/mL	823.22	407 [176-823]	382 [177-1021]	0.99
HbA1c (%)	6.13 ± 1.36	5.53 ± 0.50	7.42 ± 1.69	< 0.001
Medication at discharge				
Aspirin, n (%)	323 (99%)	222 (99%)	97 (100%)	0.25
Clopidogrel/Ticagrelor, n (%)	316 (97%)	217 (96%)	95 (98%)	0.48
Statin, n (%)	312 (96%)	215 (96%)	93 (96%)	0.90
B-Blocker, n (%)	297 (91%)	203 (90%)	90 (93%)	0.46
ACEI/ARB, n (%)	233 (72%)	155 (70%)	74 (76%)	0.22
Diuretic, n (%)	21 (7%)	9 (4%)	12 (12%)	0.005
MRA, n (%)	6 (2%)	3 (1%)	3 (3%)	0.29

Caption: BMI, Body Mass Index; HF, Heart Failure; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; OSA, Obstructive Sleep Apnea; ACS, Acute Coronary Syndrome; STEMI, ST Segment Elevation Myocardial Infarction; LAD, Left Anterior Descending Artery; RCA, Right Coronary Artery; LCx, Left

Circumflex Artery; PCI, Percutaneous Coronary Intervention; GFR, Glomerular Filtration Rate; Hb, Hemoglobin; CK, Creatine Kinase; TnT, Troponine T; Pro-BNP, Pro-B-type natriuretic peptide; ACEI/ARB, Angiotensin-converting-enzyme Inhibitor/Angiotensin II Receptor Blocker; MRA, Mineralocorticoid Receptor Antagonist.

Table II – Echocardiographic features of studied patients.

Characteristic	Overall (n=336)	Non-diabetic patients (n=227)	Diabetic patients (n=99)	P-value
LV mass indexed, g/m2	103.4 ± 23.0	103.11 ± 23.0	103.61 ± 23.2	0.87
LVEDD, mm	46.20 ± 4.77	46.42 ± 4.71	45.64 ± 4.92	0.21
LVESD, mm	30.00 ± 5.01	30.22 ± 5.40	29.47 ± 3.85	0.33
LA diameter, mm	38.66 ± 4.64	38.34 ± 4.90	39.39 ± 3.87	0.08
LA area, cm2	20.12 ± 3.97	19.98 ± 4.18	20.42 ± 3.44	0.40
LA volume, cm2	59.59 ± 15.66	59.32 ± 17.71	60.06 ± 11.74	0.88
Segmental motion abnormalities				
Anterior, n (%)	89 (28%)	67 (30%)	20 (21.7%)	0.12
Posterior, n (%)	141 (45%)	99 (45%)	41 (45%)	1.00
Inferior, n (%)	178 (57%)	125 (57%)	52 (57%)	0.99
Moderate/severe MR, n (%)	11 (4%)	8 (4%)	3 (3%)	0.86
PSAP	25.82 ± 5.62	25.46 ± 5.43	26.70 ± 6.08	0.21
RV systolic dysfunction, n (%)	8 (3%)	6 (3%)	2 (2%)	0.78
LV remodelling pattern				
Normal, n (%)	76 (23%)	61 (27%)	15 (15%)	
Concentric, n (%)	123 (37%)	82 (36%)	41 (41%)	

Concentric LVH, n (%)	109 (33%)	66 (29%)	36 (36%)	0.08
Eccentric LVH, n (%)	24 (7%)	17 (8%)	7 (7%)	

Caption: IVS, Interventricular Septum; PWT, Posterior Wall Thickness; LVEDD, Left Ventricular End Diastolic Diameter; LVESD, Left Ventricular End Sistolic Diameter; LA, Left Auricle; MR, Mitral Regurgitation; LV, Left Ventricle; LVH, Left Ventricular Hypertrophy.

Table III – Association of diabetic status and composite outcome.

	Non-diabetic			Diabetic			Dichotomous	
	N	**Events**	**Event Rate/100 person years (95% CI)**	**N**	**Events**	**Event Rate/100 person years(95% CI)**	**HR (95% CI)**	**P-value**
Unadjusted	2559	199	2.30(2.00-2.65)	595	84	4.40(3.56-5.46)	1.91 (1.48-2.47)	<0.001
Adjusted for age and sex							1.68 (1.30-2.18)	<0.001

FIGURE 1 – Survival curves according to diabetic status (p=0.002).